THRESHOLDS OF RESPONSE OF THE CEREBRAL VESSELS OF MAN TO INCREASE IN BLOOD CARBON DIOXIDE

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NAVAL AIR STATION

PENSACOLA, FLORIDA

U. S. Naval School of Aviation Medicine January 1954

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11 pp. 2 tables 2 figures UNCLASSIFIED

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Report by

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5 January 1954

SUMMARY[1]

1. The cerebral vascular responses in man to inhalation of 2.5% and 3.5% CO_2 have been studied in 21 subjects. The findings are compared with those obtained by others with higher concentrations of carbon dioxide.

2. The vasodilator response to increase in arterial CO_2 tension appears to be a threshold type of phenomenon. A mean increase in arterial CO_2 tension of less than 4.7 mm. Hg does not affect cerebral blood vessels; each increase above this value is associated with progressive vasodilatation. No data is available beyond an increase in pCO_2 of 14 mm. Hg. A mean increase in arterial pCO_2 of 5.5 mm. Hg produced a slight but, it is believed, physiologically significant vasodilatation.

3. With constant cerebral metabolism, a reduction in cerebral blood flow of approximately 30% would be required to raise end-capillary and venous CO_2 tension to the vasodilator threshold. It is probable that cerebral vessels dilate with a smaller reduction in blood flow, owing to the combined effects of increased pCO_2 and reduced pO_2.

4. Carbon dioxide in 3.5% concentration has little effect on the blood pressure in most patients when inhaled for periods up to 30 minutes. It produces considerably less dyspnea than 5% CO_2 and may have applications in the treatment of certain states of cerebral vascular insufficiency.

INTRODUCTION

The level of carbon dioxide in the blood is now generally accepted as one of the major factors in the regulation of the cerebral circulation. It was first shown in experimental animals that increase in blood carbon dioxide exerts a vasodilator effect on cerebral blood vessels (1,2). Similar effects were postulated in man by Lennox and Gibbs (3) on the basis of decrease in the cerebral arteriovenous oxygen difference. Conclusive evidence of the effects of carbon dioxide on cerebral blood flow in man was provided by the experiments of Kety and Schmidt with the nitrous oxide method. Reduction in arterial CO_2 through hyperventilation was shown to produce a decrease in blood flow (4), whereas increase in arterial CO_2 through inhalation of 5% and 7% carbon dioxide was found to cause a striking increase in blood flow (5).

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The above observations on man, which were concerned with large-scale effects, do not in themselves permit a precise formulation of the role of carbon dioxide in the control of the cerebral circulation. The minimal changes in blood CO_2 which will evoke vascular responses must be known, together with the degrees of response which are produced by given increments of change in CO_2 beyond these threshold values. Knowledge of the minimal increase in arterial CO_2 required to dilate cerebral vessels has potential therapeutic application in the treatment of certain states of severe impairment of blood flow to the brain. Carbon dioxide in 5% or greater concentration has the disadvantages of raising blood pressure (5,6) and producing uncomfortable dyspnea within a relatively few minutes (7). It appeared possible, however, that some lower concentration of carbon dioxide might prove more tolerable, while still retaining vasodilator properties.

The present studies were concerned with the thresholds of response of the cerebral vessels of man to increase in blood carbon dioxide. Cerebral blood flow determinations were made with the nitrous oxide method, employing concentrations of 2.5 and 3.5% CO_2 in the inspired gas. Data on the associated changes in blood gases and pH are given.

METHODS

The subjects for these studies were hospital patients convalescing from a variety of illnesses in which the brain was not involved. Seven patients were given 2.5% CO_2 and 14 patients 3.5% CO_2 in the inspired gas. The mean ages of these two groups were 32 and 36 years, respectively. Cerebral blood flow (CBF) before and during carbon dioxide inhalations was determined by the nitrous oxide method (8) with slight modifications (9). Six of the 21 patients were studied by measurements of cerebral arteriovenous gas differences alone. Cerebral oxygen consumption ($CMRO_2$) was determined from the cerebral blood flow multiplied by the cerebral arteriovenous oxygen difference, $(A-V)_{O_2}$. The values for $(A-V)_{O_2}$ were obtained from analyses of arterial and internal jugular blood samples drawn just before and just after the cerebral blood flow procedure and pooled. The cerebral vascular resistance (CVR) was calculated by dividing the blood flow into the mean arterial pressure, measured from either the femoral or brachial arteries with a damped mercury manometer.

Control observations of the cerebral circulation were made with the standard gas mixture for the nitrous oxide method (15% N_2O, 21% O_2, 64% N_2). Following this the patient was given a mixture containing either 2.5% or 3.5% CO_2, with 21% O_2 and the remainder N_2. At the end of 15 to 20 minutes this mixture was changed to gas containing the same percentages of CO_2 and O_2, together with 15% N_2O, and the experimental blood flow determination carried out.

The pooled blood samples of arterial and venous blood were analyzed for oxygen and carbon dioxide content by the combined procedure for these gases described by Peters and Van Slyke (10), as modified for the presence of nitrous oxide by Kety and Schmidt (8). Oxygen capacity of the blood samples was determined by the method of Roughton and Darling (11). Blood

pH was measured with a Cambridge Model R. pH meter, with appropriate corrections to body temperature (12). Carbon dioxide tensions (pCO_2) were obtained from the pH, CO_2 content and hematocrit by means of the nomogram of Singer and Hastings (13). Venous oxygen tension was determined from the pH and the percent of oxygen saturation, using the oxygen-hemoglobin dissociation curves of Dill (14). Observations were made on the character of the subject's breathing, but respiratory minute volumes were not measured.

RESULTS

Inhalation of 2.5% carbon dioxide produced very little change in the mean values of the cerebral blood flow, oxygen consumption or vascular resistance (Table I). The blood pH and gas tensions were not determined in this group, but a comparable group of 7 subjects given 2.5% CO_2 for 15 minutes showed a decrease in the mean value for arterial pH from 7.37 to 7.34 and an increase in arterial pCO_2 from 41.3 to 45.6 mm. Hg. Dyspnea and increase in rate or depth of the subjects' breathing were either slight or not detectable. The same concentration of carbon dioxide was also well tolerated by 10 patients with cerebral vascular accidents (7) for periods of 30 minutes to one hour.

Carbon dioxide in 3.5% concentration was associated with small but statistically insignificant increase in the cerebral blood flow (Table I). There was almost no change in either the cerebral oxygen consumption or cerebral vascular resistance. There were, however, decreases in the cerebral arteriovenous oxygen difference. The mean values of $(A\text{-}V)_{O_2}$ for air and CO_2 breathing in the patients studied by the nitrous oxide method were 5.8 and 5.3 volumes percent, respectively. In the larger group of 14 subjects the mean value for $(A\text{-}V)_{O_2}$ was 6.3 volumes percent with air and 5.3 volumes percent with CO_2 breathing ($p = .1$). Nine of these subjects showed a fall in $(A\text{-}V)_{O_2}$ of 0.5 volumes percent or more; four showed little change; and only one subject had an increase in this function (Table II). Changes in the blood gas tensions and pH in the five patients of the nitrous oxide group in whom these functions were studied differed only slightly from those in the larger group of nine subjects (Table II). In these nine individuals 3.5% carbon dioxide produced the following increases: arterial pCO_2, 5.5 mm. Hg; jugular venous pCO_2, 4.2 mm. Hg; jugular venous pO_2, 4.1 mm. Hg. Arterial pH fell .04 units and jugular venous pH .03 units with this concentration of carbon dioxide.

A definite deepening and slight increase in rate of respiration was usually observed 10 to 15 minutes after onset of inhalation of 3.5% CO_2. This was associated with slight dyspnea, which in a few patients had become definitely uncomfortable 30 minutes after breathing the gas mixture.

The relation on the concentrations of CO_2 in the inspired gas to the cerebral arteriovenous oxygen difference is shown in Figure 1. The data for 5% and 7% CO_2 are from the work of Kety and Schmidt (5). Supplementary observations made with 5% CO_2 in our laboratory (7) in four patients with cerebral vascular accidents showed a decrease in $(A\text{-}V)_{O_2}$ only slightly less

than that observed by Kety and Schmidt in normal subjects. It is evident in Figure 1 that a rather abrupt change in the slope of the curve occurs between 2.5 and 3.5% carbon dioxide. The striking fall in the arteriovenous oxygen difference with each additional increment in the concentration of inspired CO_2 is also quite apparent.

In the present studies and those of Kety and Schmidt the cerebral oxygen remained unchanged during the inhalation of various concentrations of carbon dioxide. Since $CBF = \frac{CMR_{O_2}}{(A\text{-}V)_{O_2}}$, and with CMR_{O_2} a constant, the blood flow in this group of subjects will vary as to reciprocal of the arteriovenous oxygen difference. The relationship between $\frac{1}{(A\text{-}V)_{O_2}}$ and the change in mean arterial CO_2 tension with the different inspired CO_2 concentrations is illustrated in Figure 2. The data of Kety and Schmidt in this figure show a mean increase in arterial pCO_2 of 7 mm. Hg with 5% CO_2, and 14 mm. Hg with 7% carbon dioxide. The value for $\frac{1}{(A\text{-}V)_{O_2}}$ abruptly rises beyond an apparent threshold value and continues to rise rapidly with further increase in pCO_2 up to 14 mm. Hg. A doubling of blood flow is predicted for a 10 to 11 mm. Hg increase in CO_2 tension. If the ascending part of the curve is extrapolated downward, it crosses the horizontal portion of the curve at 4.7 mm. Hg. A similar plot of the cerebral blood flow, determined from the nitrous oxide concentration, as a percentage of its control value yields an S-shaped curve which crosses the control level (100%) at 5.3 mm. Hg. The CBF_{N_2O} points are lower than the corresponding $\frac{1}{(A\text{-}V)_{O_2}}$ values in the 3.5% and 7% CO_2 observations, and higher in the case of the 5% CO_2 studies.

DISCUSSION

The findings with 2.5% CO_2 clearly indicate that the threshold for cerebral vasodilator effect lies beyond this inspired concentration and its associated mean increase in arterial CO_2 tension of 4.3 mm. Hg. This conclusion is based on the absence of changes in the cerebral blood flow, vascular resistance and arteriovenous oxygen difference.

In regard to 3.5% CO_2 the question must first be considered as to which determination possesses the greater validity, under the conditions of the present experiment, for the detection of small changes in blood flow: the cerebral arteriovenous oxygen difference or the nitrous oxide method. Actually, the validity of change in $(A\text{-}V)_{O_2}$ as a measure of change in CBF rests upon the demonstration that cerebral oxygen consumption, as determined by the nitrous oxide method, is not altered by inhalation of carbon dioxide over the concentration range of 2.5 to 7%. There seems little reason to

question the constancy of the $CMRO_2$ under these circumstances, since the number of subjects in the present series combined with those studied by Kety and Schmidt is relatively large. Random errors would tend to be averaged out, and even systematic errors would not preclude correct conclusions regarding the constancy of cerebral metabolism. If the $CMRO_2$ is a constant, blood flow will vary as $\frac{1}{(A\text{-}V)_{O_2}}$, and this function may be used as a measure of change in flow. In a limited series of studies, such as the present observations with 2.5 or 3.5% CO_2, the $(A\text{-}V)_{O_2}$ determined by Van Slyke gasometric analysis is probably the more accurate measure of small changes in blood flow. The nitrous oxide method in any given determination contains more possibilities of error, since it involves multiple analyses, the assumption of equilibrium in respect to nitrous oxide between the brain and jugular venous blood, and other potential sources of error. In the present studies, somewhat greater reliance will be placed on the arteriovenous oxygen difference, although similar conclusions except for quantitative differences can be drawn from the nitrous oxide data.

The relationships shown in Figure 2 indicate that the cerebrovascular response to increase in arterial CO_2 tension is a threshold type of phenomenon. This is demonstrated by the absence of change in $\frac{1}{(A\text{-}V)_{O_2}}$ over the lower range of increase in pCO_2, then an abrupt change in the slope of the curve followed by progressive increase in $\frac{1}{(A\text{-}V)_{O_2}}$ with further increase in arterial CO_2 tension. Since mean arterial blood pressure was unaffected by 3.5% CO_2 (Table I) and only slightly to moderately affected by 5 and 7% CO_2 (5), the rising curve of cerebral blood flow with increase in arterial CO_2 tension beyond the threshold value must have been primarily due to progressive dilatation of cerebral blood vessels.

Two types of threshold can usefully be defined for this phenomenon: (1) that value for increase in arterial pCO_2 below which there is no effect on cerebral vessels and above which there is increasing cerebral vasodilatation; and (2) that amount of pCO_2 increase which is accompanied by changes in the cerebral circulation of a significant or specified magnitude.

The probable mean threshold in the first sense can be obtained by extrapolating the rising portion of the curve backward to its intersection with the control (100%) level, which yields a value of 4.7 mm. Hg. The arteriovenous O_2 difference for the 5% CO_2 cases (mean increase in arterial pCO_2 7 mm. Hg) is significantly ($p < .05$) different from the control value and falls just short of significance for the 3.5% CO_2 group (mean increase in arterial pCO_2 5.5 mm. Hg). Obviously, the nearer a point on the curve of Figure 2 lies to the threshold value of pCO_2 change, the less will be the statistical significance of the corresponding $(A\text{-}V)_{O_2}$ or $\frac{1}{(A\text{-}V)_{O_2}}$ compared with their control values.

The threshold in the second sense is chosen as the average increase in arterial pCO_2 which was produced by 3.5% carbon dioxide, namely, 5.5 mm. Hg. The conclusion that this mean increase of pCO_2 produced a slight but physiologically significant vasodilatation is based on several considerations. As stated earlier, in the 14 subjects given this concentration of 3.5% CO_2, the arteriovenous O_2 difference showed a decrease in nine instances, was little changed in four, and increased in only one case. The standard errors of $\frac{1}{(A\text{-}V)_{O_2}}$ for the points representing the mean increase in arterial pCO_2 produced by 2.5 and 3.5% CO_2 do not overlap. The p value of 0.1 falls only slightly short of significance ($p = .05$ or less). A further mean increase of only 1.5 mm. Hg was associated with a statistically significant increase in cerebral blood flow and significant decrease in arteriovenous oxygen difference (5). The 42% increase in $\frac{1}{(A\text{-}V)_{O_2}}$ associated with 5% CO_2 breathing and its 7 mm. Hg mean increase in arterial pCO_2 is beyond the small but physiologically significant change which we are seeking. Internal jugular venous pO_2 was raised by 4.1 mm. Hg during the CO_2 breathing, a finding consistent with vasodilatation.

Although the thresholds defined above have been stated in terms of change in arterial pCO_2, it is possible that they actually represent thresholds for the effects of associated change in hydrogen ion or bicarbonate ion concentration. The work of Schieve and Wilson (15) appears to rule out the H-ion as a possible vasodilator, but does not eliminate the HCO_3-ion. The question must also be raised as to whether we are dealing with a "pure" CO_2 threshold or whether an increase in oxygen tension as a result of hyperventilation was a factor. Cerebral vessels are only slightly constricted by 50% oxygen (16), which should produce an arterial pO_2 of nearly 300 mm. Hg, calculated from the alveolar equation (17) and an assumed alveolar-arterial pO_2 gradient of 20 mm. of mercury. Since the inspired pO_2 itself was only 159 mm. Hg, the possibility that change in arterial pO_2 influenced the results seems remote.

The site of action of the carbon dioxide in these experiments was probably the blood vessels themselves. Although a vasodilator innervation has been demonstrated in the experimental animal (18), its functional significance for man is unknown. It is of interest that recent experiments suggest that a threshold concentration of CO_2 is required for respiratory stimulation (19). Observations have been made on the effect of an increase in blood CO_2 on other vessels of the body deprived of their vasomotor innervation. The vessels in sympathectomized upper extremities in man (20) and the hind limb vessels in dogs, given ganglionic-blocking doses of tetraethylammonium (21), respond alike by vasodilatation to an increase in blood carbon dioxide.

The CO_2 tension thresholds for cerebral vascular effect which have been reported in this paper are non-specific in the sense that they do not indicate which type of vessel is responding: arteries, arterioles, capillaries or venules. Since the increase in venous pCO_2 during 3.5% CO_2 breathing (4.2 mm. Hg) was almost as great as that of arterial pCO_2, the thresholds as

given would not be greatly different, regardless of which type of vessels is dilating. As a corollary we may conclude that, if all of these vessels are responding, the threshold is very nearly the same throughout the group. In the case of arteriosclerotic cerebral blood vessels, it might be anticipated that their threshold of response to CO_2 change is different from normal vessels. They have been shown to respond poorly to 5% CO_2 inhalation (22).

Studies on dogs by Gurdjian and co-workers (23) furnish evidence on the relationship between cerebral $(A\text{-}V)_{O_2}$ and arterial pCO_2 beyond the range of values available for acute experiments in man (Fig. 1). These workers found that an actual value of 70 mm. Hg arterial pCO_2 apparently was sufficient to drive the cerebral vasodilator mechanism close to its limit of response. It seems reasonable to anticipate a similar leveling off of the vasodilator response in man with progressively higher values of arterial CO_2 tension.

In the intrinsic control of the cerebral circulation, carbon dioxide and oxygen tension changes would operate simultaneously, either additively or in competition. The threshold for combined fall in pO_2 and rise in pCO_2, a situation produced by decrease in cerebral blood flow, may occur at a lower pCO_2 than the threshold reported in this paper. From the Fick equation and the blood nomogram (13), it can be shown that cerebral blood flow must fall by approximately 30% to raise venous pCO_2 to the vasodilator threshold. Actually, cerebral vessels dilate with a smaller reduction in blood flow. Studies on such combined thresholds, and on the threshold of cerebral vascular response to reduction in blood CO_2 tension, are obviously needed. The data in the existing literature on the combined effects of arterial pCO_2 and pO_2 on cerebral blood flow has recently been worked into a useful nomogram by Cannon (24).

Therapeutic applications of our findings remain to be explored. It would appear that 3.5% CO_2 may be of value in the treatment of cerebral vascular manifestations produced by a reduction in blood flow. Although more weakly vasodilator than 5% CO_2, it is considerably more tolerable from the standpoint of dyspnea and can be given for 30 minutes in most patients without producing excessive dyspnea or changes in arterial blood pressure. Its use in selected patients with cerebral vascular insufficiency seems indicated.

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TABLE I

CEREBRAL FUNCTIONS AND BLOOD STUDIES DURING AIR AND CARBON DIOXIDE BREATHING

%	Pt.	Age	CBF cc./100 Gm./min. Air	CBF cc./100 Gm./min. CO_2	$CERO_2$ cc./100 Gm./min. Air	$CERO_2$ cc./100 Gm./min. CO_2	CVR mm.Hg/cc./100 Gm./min. Air	CVR mm.Hg/cc./100 Gm./min. CO_2	Mean Art. Pressure mm.Hg Air	Mean Art. Pressure mm.Hg CO_2	A-V Oxygen vol.% Air	A-V Oxygen vol.% CO_2	Hemato-crit	Art. pH Air	Art. pH CO_2	Art. pCO_2 mm.Hg Air	Art. pCO_2 mm.Hg CO_2	Venous pH mm.Hg Air	Venous pH mm.Hg CO_2	Venous pCO_2 mm.Hg Air	Venous pCO_2 mm.Hg CO_2	Venous pO_2 mm.Hg Air	Venous pO_2 mm.Hg CO_2
2.5% CO_2	W.M.	21	50	49	2.9	2.9	2.1	2.1	107	105	5.7	6.0	45	-	-	-	-	-	-	-	-	-	-
	E.H.	29	45	61	2.1	3.1	1.6	1.2	73	74	3.7	5.1	38	-	-	-	-	-	-	-	-	-	-
	M.S.	53	51	53	2.3	2.5	1.2	1.7	61	87	4.6	4.8	25	-	-	-	-	-	-	-	-	-	-
	C.D.	19	56	52	2.8	3.1	1.4	1.8	80	84	5.0	6.0	45	-	-	-	-	-	-	-	-	-	-
	V.H.	42	48	52	2.5	2.6	1.4	1.5	67	78	5.2	5.0	36	-	-	-	-	-	-	-	-	-	-
	W.H.	19	32	57	3.9	3.4	1.4	1.5	85	85	5.4	5.9	45	-	-	-	-	-	-	-	-	-	-
	T.R.	44	47	47	3.5	3.4	2.2	2.0	101	95	7.3	7.2	40	-	-	-	-	-	-	-	-	-	-
	Mean	32	51	53	2.9	3.0	1.6	1.7	82	87	5.5	5.7	39	7.36*	7.35*	41.3*	45.6*	-	-	-	-	-	-
3.5% CO_2	H.T.	23	49	63	3.1	2.5	1.5	1.3	72	78	5.2	3.9	37	-	-	-	-	-	-	-	-	-	-
	C.C.	33	49	53	3.0	2.5	1.9	1.5	91	85	8.2	4.7	40	7.39	7.32	35	45	7.32	7.28	47	57	29	37
	R.L.O.	41	68	74	2.5	3.4	1.2	1.1	81	83	3.8	4.6	27	-	-	-	-	-	-	-	-	-	-
	E.J.	48	58	53	3.2	2.7	1.9	2.1	108	109	5.6	5.1	33	-	-	-	-	-	-	-	-	-	-
	W.McL	25	51	54	3.3	3.5	1.9	1.5	94	83	6.5	8.4	47	7.38	7.30	47	55	7.30	7.25	61	70	33	35
	O.O.	40	68	72	3.3	3.4	2.1	1.8	144	128	4.8	4.7	40	7.40	7.36	43	47	7.34	7.32	52	55	34	37
	W.M.J.	36	57	54	3.0	2.9	1.6	1.8	90	98	5.1	5.3	38	7.42	7.40	37	39	7.37	7.35	46	47	35	35
	G.M.	52	30	33	2.5	2.7	3.5	3.4	110	112	8.6	8.3	44	7.40	7.35	41	45	7.33	7.29	52	54	26	27
	Mean	37	54	57	3.0	2.9	1.9	1.8	99	97	5.8	5.3	38	7.40	7.35	40.6	48.2	7.33	7.30	51.6	58.6	31.4	34.2

* *Data from 7 other Control Subjects*

TABLE II

ARTERIAL AND INTERNAL JUGULAR VENOUS CARBON DIOXIDE AND OXYGEN TENSIONS AND CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCES WITH AIR AND 3.5% CARBON DIOXIDE INHALATION

Patient	Age	Art. pCO_2 mm. Hg		Art. pH		Ven. pCO_2 mm. Hg		Ven. pH		Ven. pO_2 mm. Hg		(A-V) Oxygen Vol. %	
		Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2
C. C.	33	35	45	7.39	7.32	47	57	7.32	7.26	29	37	6.2	4.7
W. McL.	25	47	55	7.38	7.30	61	70	7.30	7.25	33	35	6.5	6.4
G. G.	40	43	47	7.40	7.36	52	55	7.34	7.32	34	37	4.8	4.7
W. M. J.	36	37	39	7.42	7.40	46	47	7.37	7.36	35	35	5.1	5.3
G. M.	52	41	45	7.40	7.35	52	54	7.33	7.29	26	27	8.6	8.3
C. P.	22	40	40	7.38	7.38	48	49	7.32	7.32	27	32	4.9	3.8
J. S.	25	42	49	7.39	7.38	51	55	7.35	7.34	35	38	5.3	4.8
C. H.	58	48	55	7.31	7.27	58	61	7.28	7.24	30	41	5.4	3.9
E. C.	37	37	45	7.43	7.37	52	57	7.35	7.32	24	28	9.6	7.8
H. T.	23	--	--	----	----	--	--	----	----	--	--	6.2	3.9
R. L. D.	41	--	--	----	----	--	--	----	----	--	--	3.8	4.6
E. J.	46	--	--	----	----	--	--	----	----	--	--	5.6	5.1
H. H.	42	--	--	----	----	--	--	----	----	--	--	7.9	5.6
F. M.	22	--	--	----	----	--	--	----	----	--	--	8.3	5.8
Mean (of first 9 patients)	36.4	41.1	46.6	7.39	7.35	51.9	56.1	7.33	7.30	30.3	34.4	6.3	5.5
Mean (of all 14)	35.9	--	--	----	----	--	--	----	----	--	--	6.3	5.3 *

* Statistical significance of difference from mean with air: $p = .1$

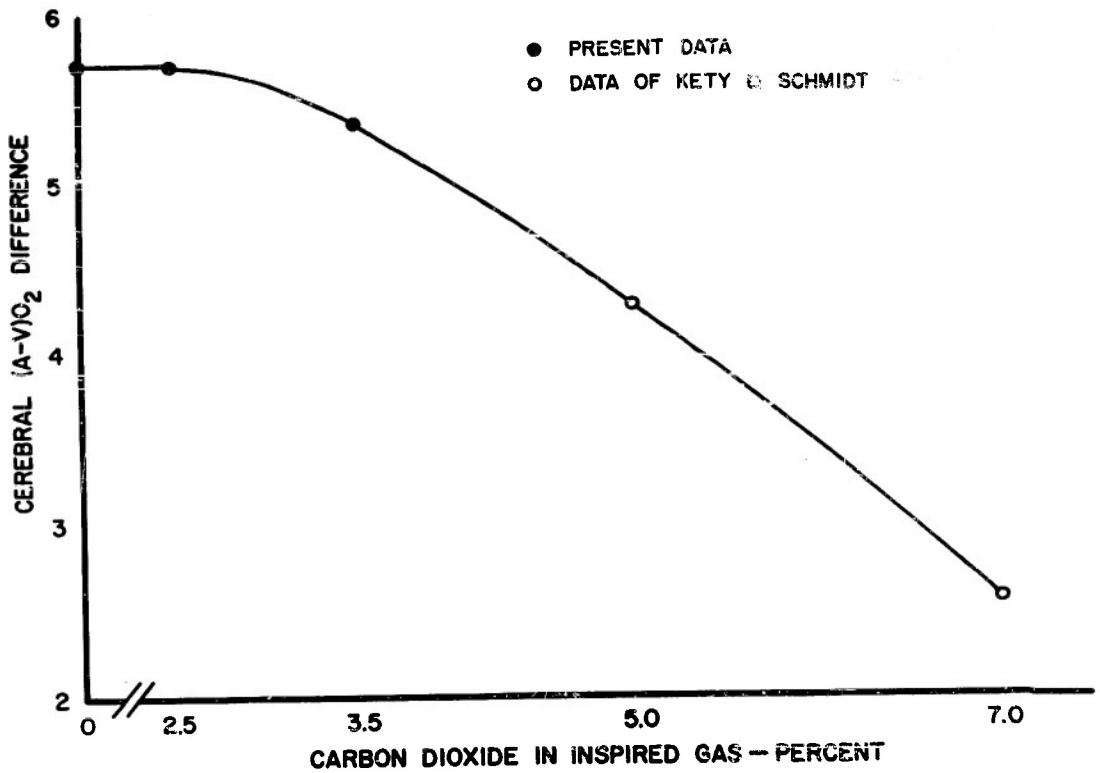

FIGURE 1

THE RELATION BETWEEN THE CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE AND THE PERCENTAGE OF CARBON DIOXIDE IN THE INSPIRED GAS

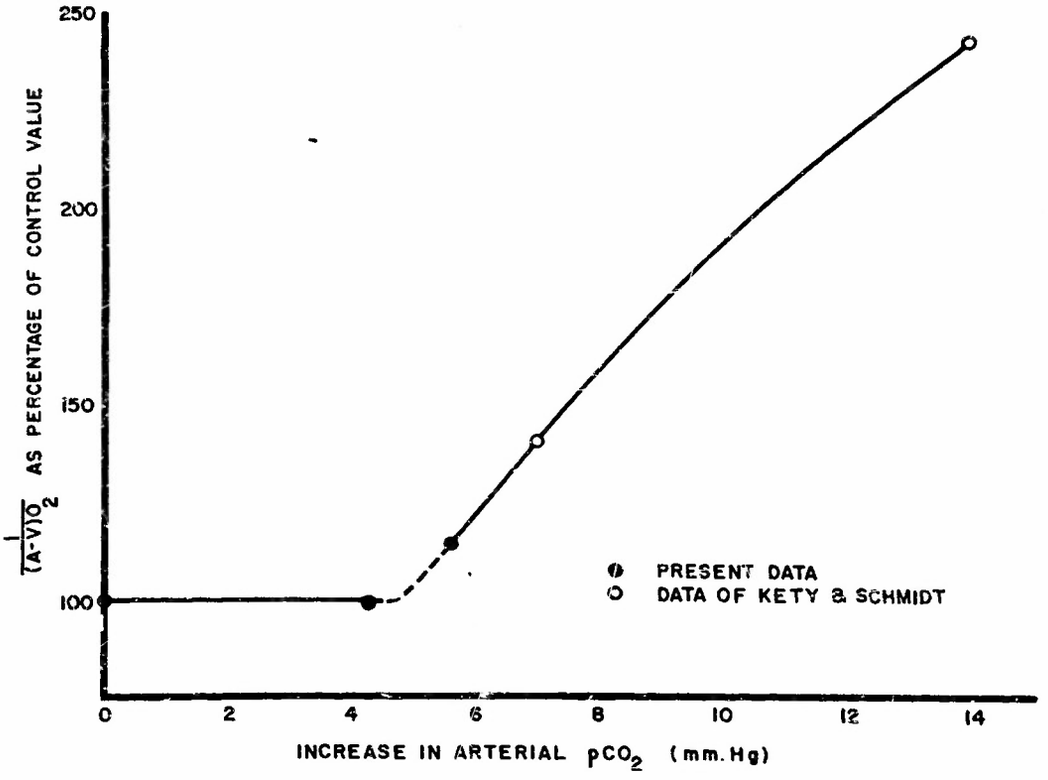

FIGURE 2

RELATION BETWEEN THE RECIPROCAL OF THE CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE AND THE INCREASE IN ARTERIAL CARBON DIOXIDE TENSION